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ENANTIOSELECTIVE RING-CLEAVAGE OF MESO-EPOXIDES WITH 171

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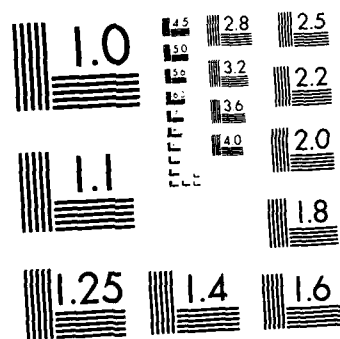
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Enantioselective Ring-cleavage of *meso*- Epoxides  
with B-Halodiisopinocampheylboranes

by

N. N. Joshi, M. Srebnik, and Herbert C. Brown

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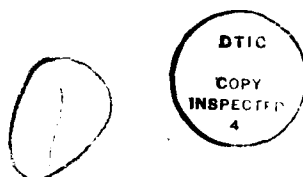
## ABSTRACT

### Enantioselective Ring-Cleavage of *meso*-Epoxides with B-Halodiisopinocampheylboranes.

N. N. Joshi, M. Srebnik, and H. C. Brown\*

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Abstract: B-Halodiisopinocampheylboranes,  $\text{Ipc}_2\text{BX}$ , in particular the bromide **1b**, and the iodide **1c**, differentiate between the enantiotopic C-O bonds of *meso*-epoxides to furnish 1,2-halohydrins of moderate to excellent enantiomeric purity. Thus (-)-(1R, 2R)-2-bromocyclohexanol, (-)-(1R, 2R)-2-iodocyclohexanol, (-)-(1R, 2R)-2-iodocyclohex-4-en-1-ol and (-)-(1R, 2R)-2-bromocyclohex-4-en-1-ol are obtained in 84%, 91%, 63% and 95% ee respectively from the corresponding *meso*-epoxides and haloborane reagents. Simple recrystallization from pentane then gives halohydrins of essentially 100% ee; *cis*-2-butene oxide and *cis*-3-hexene oxide furnish the corresponding (1R, 2R)-iodohydrins in 78 and 69% ee respectively. In all cases the S carbon of the *meso*-epoxide is selectively cleaved. This is the first example of enantioselective ring cleavage of *meso*-epoxides to obtain optically active 1,2-halohydrins. (Epoxides, Boranes, *ng*)



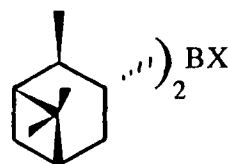
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## Enantioselective Ring-Cleavage of *meso*-Epoxides with B-Halodiisopinocampheylboranes.

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Asymmetric synthesis starting from *meso*-compounds is an increasingly important method for the preparation of optically active compounds. Various chemical<sup>1</sup> and enzymatic<sup>2</sup> procedures have been utilized for such transformations. Surprisingly, not much attention has been given to the enantioselective ring-cleavage of *meso*-epoxides which would lead to several classes of important compounds. We now report the synthesis of optically active 1,2-halohydrins using B-halodiisopinocampheylboranes, Ipc<sub>2</sub>BX (1a-c).



1a X= Cl

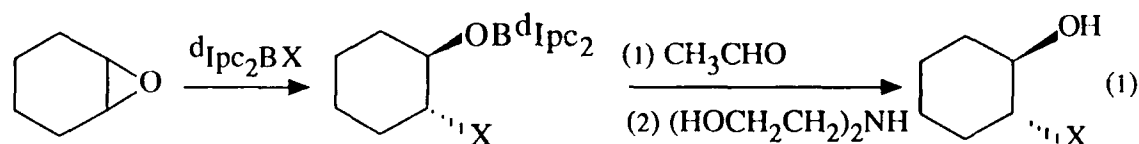
1b X= Br

1c X= I

The cleavage of carbon-oxygen bonds with boron reagents, in particular with trihaloboranes, is a well documented and established procedure<sup>3</sup>. However, the high Lewis acidity of trihaloboranes and their tridentate nature can result in the unwanted rupture of bonds in compounds containing other sensitive functional groups. To increase the selectivity in carbon-oxygen bond cleavage, monohaloboranes in which two of the halogens on boron are replaced by alkyl<sup>4</sup>, alkoxy<sup>5</sup>, thioalkyl<sup>6</sup>, or nitrogen containing<sup>7</sup> groups have recently been introduced. Such reagents indeed are selective and could by the proper choice of substituents cleave specific C-O bonds<sup>7</sup>. Recently Guindon and co-workers reported<sup>4</sup> the stereospecific ring-

cleavage of various cyclic ethers with B-bromodimethylborane. Of particular consequence in the cleavage of epoxides with these type of reagents is the fact that the halohydrin products are consistent with a predominantly  $S_N2$  type mechanism proposed for such reactions<sup>4,7,8</sup>. This suggests that the asymmetric version should proceed with a high degree of enantiotopic differentiation of the C-O bonds of suitable *meso*-epoxides. Recently, the enantioselective cleavage of cyclohexene oxide with thiols and azides in the presence of zinc or copper tartrates has been successfully accomplished<sup>9</sup>. Except for this report, the cleavage of epoxides with chiral Lewis acids is an unexplored reaction. As part of our efforts in the field of asymmetric synthesis<sup>10</sup>, we are currently exploring reactions involving boron based chiral Lewis acids. The present communication describes our investigations on the enantioselective ring-opening of some *meso*-epoxides with B-halodiisopinocampheylboranes ( $\text{Ipc}_2\text{BX}$ )<sup>11</sup>, both enantiomers of which are readily available from either (+)- or (-)- $\alpha$ -pinene.

First we examined the reaction between cyclohexene oxide and  $d\text{Ipc}_2\text{BX}$  (the superscript "d" indicates that the reagent is derived from (+)- $\alpha$ -pinene) under various conditions, i.e., temperature, solvent and molarity. Due to the labile nature of the products, a non-oxidative work-up was developed (eq 1).

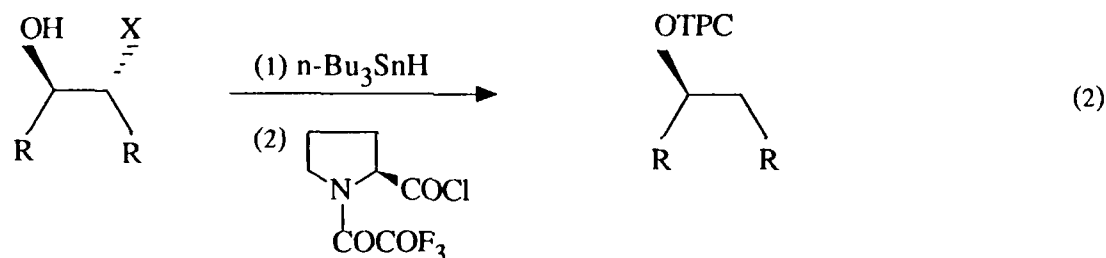


The course of the reaction was followed by  $^{11}\text{B}$ -NMR<sup>12</sup>. The reaction is very fast (<5 min) but proceeds with poor induction at  $0^\circ\text{C}$ . Not surprisingly, an inverse relationship between enantiomeric excess (% ee) and the reaction temperature was found to exist. It was established that  $\text{Ipc}_2\text{BCl}$ ,  $\text{Ipc}_2\text{BBr}$  and  $\text{Ipc}_2\text{BI}$  require  $-78^\circ\text{C}/3\text{ h}$ ,  $-100^\circ\text{C}/2\text{ h}$  and  $-100^\circ\text{C}/0.5\text{ h}$  respectively to furnish good enantioselection. Furthermore, the reaction is independent of solvent or molarity. Since **1b** and **1c** provided superior results (at least in

the case of cyclohexene oxide), we used these reagents subsequently for the preparation of optically active halohydrins (Table I).

In general [4.1.0]-oxaheptanes gave excellent initial optical yields of halohydrins<sup>13</sup>. We also found that by simple recrystallization from pentane, these could be upgraded to products of essentially 100 % ee. Cyclopentene oxide gave reduced chemical as well as optical yields. Simple acyclic epoxides were cleaved with optical inductions intermediate between those realised<sup>14</sup> for the oxides of cyclohexene and cyclopentene. The % ee of the halohydrins (as their acetates) was determined using a chiral capillary GC column, Ni(HFB-1R-Cam)<sub>2</sub><sup>15</sup>.

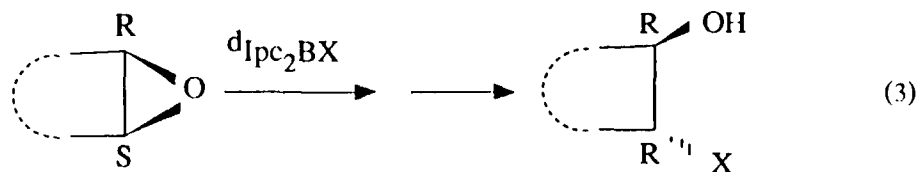
The absolute configuration of the cyclic halohydrins was determined where possible by X-ray crystallography. The absolute configuration of the acyclic compounds was elucidated as follows (eq 2).



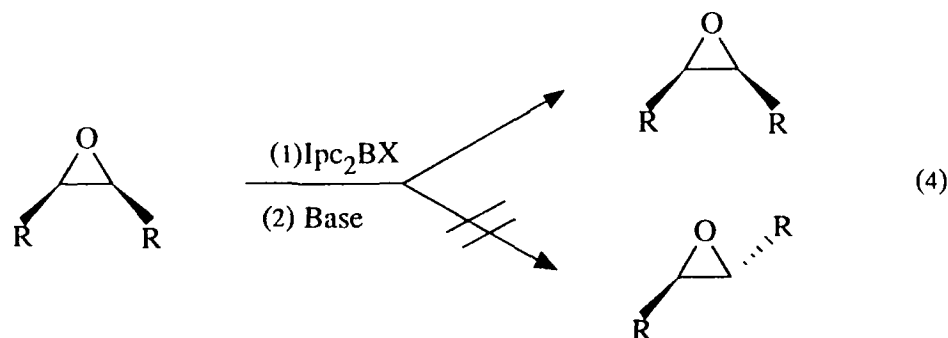
Dehalogenation with tributyltin hydride gave the known *secondary* alcohols<sup>16</sup> which were analysed as their TPC-derivatives<sup>17</sup> using capillary GC. Since the *meso*-epoxides are opened in an antiperiplanar manner, determination of the absolute configuration of one asymmetric center establishes the configuration of the other as well.

Of particular significance of this procedure is the fact that in addition to high optical induction<sup>18</sup>, the bond cleavage occurs in the same absolute sense to furnish (1R, 2R)-halohydrins in all cases examined, with  $dIpc_2BX$ <sup>19</sup> These results are consistent with the cleavage occurring in an *anti* manner with inversion at the S carbon of the *meso*-epoxides (eq 3).





In addition, closure of the acyclic chiral non-racemic halohydrins yield the starting compounds, viz. a *cis*-epoxide, which would not be the case had the opening proceeded in a *syn* manner (eq 4).



In conclusion, the present methodology demonstrates the feasibility of cleaving *meso*-epoxides in an enantioselective manner either at the R or S carbon by selecting the appropriate chiral organoborane reagents. The transformation is general, providing highly valuable difunctionalized compounds in good to excellent enantiomeric purity from simple olefins. Synthesis of optically active halohydrins is but one of the many possible applications which we are currently exploring.

**Acknowledgment:** This work was supported in part by the Office of Naval Research. We thank Dr. Phil Fanwick for the X-ray crystallographic analysis.

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- (11)  $\text{Ipc}_2\text{BCl}$  and  $\text{Ipc}_2\text{BBr}$  were prepared by passing HCl or HBr through a suspension of optically pure  $\text{Ipc}_2\text{BH}$  in pentane at  $0^\circ\text{C}$ .  $\text{Ipc}_2\text{BI}$  was made by reaction with  $\text{I}_2$ . All the reagents were recrystallized and stored as stock solutions in pentane.
- (12) The reaction is quenched with pyridine which coordinates with the unreacted haloborane ( $\delta = 18\text{-}20$  ppm) and not with the borinate ( $\delta \approx 54$  ppm) formed during the course of the reaction.
- (13) **The preparation of (1R, 2R)-(-)-2-iodocyclohexanol:** A 100 ml flask protected with a positive pressure of nitrogen, was charged with  $\text{Ipc}_2\text{BI}$  (11 mmol, 0.25 M in pentane). The solution was cooled to  $-100^\circ\text{C}$  and treated dropwise with cyclohexene oxide (10 mmol) dissolved in pentane (2 ml). After stirring for 1 h at  $-100^\circ\text{C}$ ,

the reaction was quenched by the addition of acetaldehyde (1.8 ml, excess). The mixture was allowed to warm gradually to room temperature and stirred for an additional 1 h. By that time  $^{11}\text{B}$ -NMR indicated clean formation of boronate [ $\text{R}^*\text{OB}(\text{OEt})\text{Ipc}$ ,  $\delta = 31$  ppm]. The reaction mixture was diluted with pentane (50 ml) and treated with diethanolamine (12 mmol, 4 M in THF). After stirring for 30 min, the precipitated boronate-diethanolamine complex was filtered off, the filtrate was washed with water, brine, and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solution was concentrated under reduced pressure, and the residue purified by column chromatography followed by crystallization from pentane to provide the title compound (Table I, entry 3).

(14) No attempt was made to achieve optimum results.

(15) The column is available from: CC & CC (Capillary Column Complexation Chromatography), Postfach 14, D7402, Kirchentellinsfort, F.R.G. The results of this study will be published separately.


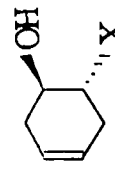
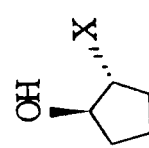
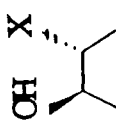
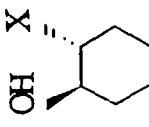
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(18) The origin of chirality in this transformation may be due to similar relative conformations of the two isopinocampheyl rings as was postulated for asymmetric hydroborations. See, Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547.

(19) The use of  $^1\text{Ipc}_2\text{BX}$  (derived from (-)- $\alpha$ -pinene) will obviously yield the corresponding (1S, 2S)-halohydrins.

Table 1. Optically Active 1,2-Halohydrins from *meso* - Epoxides and B-Halodiisopinocampheylboranes, *d*<sub>1</sub>pc<sub>2</sub>BX<sup>a</sup>

entry	epoxide	1,2-halohydrin	X	%yield <sup>b</sup>	bp °C/mmHg or mp °C	[α] <sub>D</sub> <sup>23</sup> D <sup>0</sup> (c=5, CHCl <sub>3</sub> ) (1R, 2R)	%ee <sup>c</sup>	abs. config.
1	cyclohexene oxide		Cl	70	75-80/15		22	d
2			Br	82	39-40	-26.9	84(99) <sup>e</sup>	f
3			I	89	44-45	-31.6	91(100) <sup>e</sup>	g
4	1,4-cyclohexadiene monoepoxide		Br	72	90-95/15	-42.0	63	h
5			I	75	37-38	-141.8	95(100) <sup>e</sup>	g
6	cyclopentene oxide		I	63	65-70/0.5	-5.8	52	c
7	<i>cis</i> -2-butene oxide		Br	69	75-80/15	-3.4	61	h
8			I	67	80-85/15	-15.3	78	h
9	<i>cis</i> -3-hexene oxide		Br	71	90-95/15		50	h
10			I	75	60-65/0.5	+11.8	69	h

<sup>a</sup>The superscript "d" indicates that the reagent is derived from (+)-α-pinene. <sup>b</sup>Isolated by column chromatography followed by crystallization, or bulb-to-bulb distillation. <sup>c</sup>Analysed as the corresponding acetates using Ni(HFB-1R-Cam)<sub>2</sub> capillary column. <sup>d</sup>By analogy to the other examples. <sup>e</sup>Optical purity was upgraded by recrystallization from pentane. <sup>f</sup>Bellucci, G.; Ingrosso, G.; Marioni, F.; Marsili, A; Morelli, I. *Gazz. Chim Ital.* 1974, 104, 69. <sup>g</sup>Determined by X-ray crystallography. <sup>h</sup>Elucidated through the corresponding dehalogenated product. See text.

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